WYETH-AYERST ® RESEARCH

February 7, 2000

Docket No. 99D–5047
Dockets Management Branch (HFA–305)
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

Dear Sir or Madam:

Wyeth-Ayerst hereby submits the following comments in response to the December 7, 1999 Federal Register notice (64 FR 68357) which announced the availability of a draft guidance for industry entitled: **"Draft Guidance for Industry on Pharmacokinetics in Patients With Impaired Hepatic Function: Study Design, Data Analysis, and Impact on Dosing and Labeling."**

It is our view that the recommendations made in the draft guidance are generally well supported. However, we have the following comments, which we request that the agency carefully consider before it finalizes the subject guidance. When a comment is specific to a sub-section of an identified section, this is so designated.

SECTION III: DECIDING WHETHER TO CONDUCT A STUDY IN PATIENTS WITH IMPAIRED HEPATIC FUNCTION

A. When Studies May be Important (pp. 2-3 of draft)

In general, the guidance does not seem to acknowledge that patients with hepatic impairment are, in general, fragile. Their condition (and consequently their classification by the Child-Pugh or other systems) fluctuates. In addition, because these patients' hepatic impairment is frequently a result of ethanol abuse (patients abusing alcohol may be more willing than others to participate in clinical studies), they are as a class not the most reliable study subjects.

These and other practical difficulties would argue that studies on patients with hepatic impairment should only be performed when medications are likely to be used in this population and when a biologically meaningful amount of the drug is eliminated by hepatic metabolism.

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Given this, and given the wide range of therapeutic indices which exist, we believe that a single threshold for what is considered a meaningful percentage of metabolism by the liver (>20% was proposed) may not be justifiable. For example, based on our experience, if a drug has a moderate therapeutic index it should be considered subject to biologically meaningful hepatic metabolism only when the liver is responsible for greater than 50% of its total metabolism. Therefore, we suggest that the guidance reflect that while a 20% threshold may be appropriate for drugs with very narrow therapeutic indices, a 50% threshold may be more appropriate for the larger number of drugs which have moderate therapeutic indices. The appropriate thresholds for drugs with wide therapeutic indices can only be arrived at on a case-by-case basis.

In addition, we believe that the guidance should reflect that patients with severe hepatic impairment should generally not be studied unless there is clear benefit possible for the patients in the study and/or to the patient population. Patients with grade 3 or 4 encephalopathy are often sufficiently ill that they cannot give informed consent. In addition, such studies also usually involve very few patients. Therefore, we believe that rather than studying this patient population, sponsors should be encouraged (when feasible) to take advantage of larger drug interaction studies in which the administration of inhibitors of liver metabolic pathways are used to investigate the effects of reduced liver metabolism on systemic exposure.

Finally, we note that the guidance does not recognize that drugs with narrow therapeutic indices are sometimes therapeutically monitored. Such monitoring lessens the need for clinical studies on patients with impaired hepatic function because the monitored patients' systemic exposure will be determined by the targeted therapeutic range.

B. When Studies May Not be Important (p. 3 of draft)

We believe that in the interest of clarity this section of the guidance should state that the dose-response relationship of a drug (with regard to both safety and efficacy) should be considered. For example, if a medication has a very flat dose response with respect to safety and efficacy, then it is unlikely that hepatic impairment will cause enough of a change in exposure to result in a difference in response.

IV. STUDY CONSIDERATIONS

A. Reduced Study Design (pp. 4 and 5 of draft)

Comment 1. Mild, moderate, and severe Child-Pugh categories are mentioned on page 4 of the guidance (first paragraph). It should be explicitly stated whether FDA considers mild, moderate, and severe categories of liver impairment to uniformly correspond with the Child-Pugh categories of good operative risk (class A), moderate operative risk (class B), and poor operative risk (class C) as described on page 15 (appendix) of the draft guidance.

Comment 2. We believe it would be useful for the guidance to provide some suggestions about how concomitant medications should be considered when such studies are designed.

Comment 3. We believe that comment is needed concerning when patients in a fed or fasting state should be studied.

Comment 4. ("Sample Collection and Analysis"). While it would be ideal to continue sampling long enough to characterize the terminal half-life, AUC and clearance are probably more important pharmacokinetic parameters to assess, especially if a multiple-dose design is used.

V. DATA ANALYSIS

B. Development of Dosing Recommendations (pp. 7 and 8 of draft)

For practical reasons, studies on patients with hepatic impairment are generally limited to 6-8 patients, as noted in the draft guidance. A study of this size would be unlikely to provide adequate precision to achieve a 90% confidence interval of 80-125% for AUC. Therefore, if the guidance which is finally adopted demands a 90% confidence limit, sponsors will only rarely be able to claim that hepatic impairment has no effect on a drug's PK. Given this, we suggest that more flexibility is required with respect to confidence limits.

VI. LABELLING

A. Clinical Pharmacology Section

Comment 1 (page 12, (b)(ii), "in cases of concomitant renal failure") The fundamental purpose of drug labeling is to provide physicians with information about what is known, and what is not known, about a drug. Due to practical considerations, patients with concomitant hepatic and renal impairment are only studied under special circumstances. Given this, inflexible policies requiring avoidance statements for such patients are not in the interest of this patient population or useful to the physicians who treat these challenging patients.

Comment 3 (page 12, (c)(i)). Labeling statements suggesting that doses of a drug with a wide therapeutic index should always be reduced in patients with hepatic impairment will often not be justified. Pharmacokinetic information, whether present or absent, will not change the fact that even substantial differences in exposure will not affect the response to medications with wide therapeutic indices. Therefore, we suggest that the proposed language (*would* require reduced . . . doses . . ") be changed to "*may* require reduced . . . doses . . . " Alternatively, the proposed inflexible language could be applied only to drugs with moderate therapeutic indices and the less certain language we have suggested ("*may* require") could be applied to drugs with wide therapeutic indices.

Comment 4 (page 12, (c)(ii)). Consistent with our earlier comments, a simple statement about the lack of information and the corresponding need for caution is preferred to a contraindication.

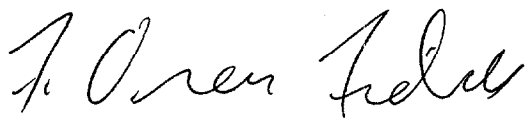
B. Precautions and/or Warnings Section (page 13)

Comment 1. In the interest of reducing ambiguity, the proposed language in the draft guidance ("consideration should be given . . ") should be changed to state that for drugs with a narrow therapeutic index a case-by-case analysis should be conducted to determine whether a statement in the warnings or precautions section is justified.

Comment 2. This section of the guidance should reflect that labeling statements concerning the need for therapeutic drug monitoring could negate the need for contraindications or warnings for patients with liver impairment. Therefore, we suggest that the following statement be added to the paragraph: "If the labeling directs that therapeutic drug monitoring is to be conducted, contraindications and/or warnings may not be necessary."

Please contact the undersigned at 610-902-3733 if you have questions or require clarification of any of the above.

Sincerely,



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